Pink Puffers vs Blue Bloaters in Asthma Too?

We would like to think that dyspnea, like pain, serves as an early-warning sign of developing disease, respiratory or cardiac. To be effective as an early-warning system, dyspnea should be absent in the absence of disease, its severity should correlate with the severity of lung function impairment, and it should be unpleasant enough to call attention to itself. However, when lung function cannot be restored to normal, it would be best for the patient if, as with pain and virtually all other sensations, a certain amount of adaptation would occur, reducing the severity of the symptom when it is chronic, so that dyspnea itself does not overshadow the underlying disease process.

However, not all dyspnea is created equal. Aside from subtle and poorly understood cultural, linguistic, and experiential differences in patients' and normal subjects' usage of terms like difficulty breathing, shortness of breath, breathlessness, chest tightness, and air hunger, issues such as adaptation to chronic loads, personality considerations, and the effects of centrally acting medications (especially narcotics and anxiolytics, but also including tricyclic antidepressants and progesterational agents) cloud the issue, making it difficult to control for all variables. Also, at least among patients with chronic obstructive lung disease, there appear to be congenital or acquired intrinsic variations in sensitivity to respiratory sensations, leading to the old concept of two types of COPD patients: "pink puffers" and "blue bloaters." Modern understanding of pathophysiology does not fully support that COPD patients with relatively normal arterial PCO₂ have higher respiratory drive and more dyspnea than do those with carbon dioxide retention—both types of patients have high respiratory drive, and the pathogenesis of dyspnea is much more complex than simply an imbalance between load and strength. Nonetheless, there is some general truth to the concept that patients with severely impaired pulmonary function may show a range of respiratory drive responses, all higher than normal, and that some such patients drive their respiratory muscles strongly enough to achieve normal PCO₂ despite severe airways obstruction, while others with no more severe obstructive disease accept carbon dioxide retention. It is also clear that patients with severe COPD who will not accept carbon dioxide retention have to apply more respiratory muscle effort to breathing and thus have lesser exercise tolerance than do those with equally severe pulmonary function impairment who, either due to "naturally occurring" or drug-induced blunting of their respiratory drive, allow their PCO₂ to climb—the former are chronically miserable with dyspnea, but they have fewer hypoxia-related complications.

In this issue of CHEST (see page 329), Magadle and associates report the results of a prospective comparison of the occurrence of near-fatal and fatal asthma among asthmatics with low, normal, or high perception of dyspnea (POD). In confirmation that the low-POD group was relatively insensitive to asthma symptoms, they found that that group averaged less than half the β₂-agonist use of the high-POD group, despite having no higher peak expiratory flow rates. They also found that mortality, near-fatal asthma attacks, and hospitalizations were confined mainly to the low-POD group.

Interestingly, examination of the data of Magadle and associates reveals that both the high- and low-POD groups had much more frequent emergency department (ED) visits (0.6 ED visits and 0.4 ED visits per patient per year, respectively) than did the normal-POD group (0.06 ED visits per patient per year), and further examination suggests a possible explanation. The high-POD group had a very low ratio of hospitalizations to ED visits (0.2), presumably because their high POD prompts severe symptoms in the absence of severe obstruction. In contrast, the low-POD group had a very high ratio of hospitalizations to ED visits (0.7), presumably because their low POD prevents symptoms until the asthma attacks are relatively advanced. Their high ED visit rate was because their absence of symptoms prevented them from recognizing and aborting asthma attacks at home.

A number of methodologic problems call into question some of the conclusions of the study and limit its appeal. For example, the patients in the...
low-POD group were, on average, 10 years older, had a 9-year-longer average duration of asthma, and had a 12% lower average percent-predicted FEV1 than did the high-POD group. The differences were not statistically significant, but we are not given a power analysis to allow us to judge how much of a type II error there might have been. The longer duration of asthma and the lower FEV1 during a period of relative stability in the low-POD group suggest that those subjects may have had more opportunity to adapt to chronic respiratory symptoms, naturally leading to lesser perception of dyspnea when challenged. It would have been better to study groups of subjects matched for age, gender, duration of asthma, and severity of disease. Similarly, thyroid status was not determined, and we are not told specifically whether patients receiving sedatives, tricyclic antidepressants, and progestational agents were included in the study population.

Also, the measurement of POD used by the authors relies on quantification of dyspnea during exposure to graded threshold loads up to $-30$ cm H2O, where the loads are quantified as absolute levels of vacuum, rather than as percentages of maximal inspiratory pressure (MIP); $-30$ cm H2O may be $\geq 50\%$ of the MIP of a normal older female subject, but $< 20\%$ of that of a young male subject. Independent of their actual abilities to perceive respiratory sensations, one would expect the normal older female subject to report severe dyspnea while the young male subject hardly notices the load. It would have been better to tailor each test to the individual subject’s MIP.

Finally, during their measurements of POD, Magadle and associates quantified each increment of load as the negative pressure generated to overcome the threshold load and related it to the subject’s estimate of dyspnea. But some asthmatic subjects have dynamic hyperinflation and consequent intrinsic positive end-expiratory pressure (PEEP)—positive alveolar pressure just at the onset of their inspiratory effort—even when well. In such cases, before they can achieve any inspiratory flow, they must use inspiratory muscle effort to bring their alveolar pressure down to atmospheric pressure, and then to the set threshold vacuum, so measuring only the inspiratory vacuuum will underestimate that effort by the amount of intrinsic PEEP. Thus, if any of these subjects had intrinsic PEEP, their POD was underestimated. It would have been better to measure intrinsic PEEP and take it into account.

Despite these substantial problems, the evidence from this study suggests that asthmatics exhibit a range of PODs, with a substantial fraction (26% of the reported population) having lower POD than that measured in normal subjects. Since the patient population was referred to a specialty clinic, we cannot assume that the 26% figure holds for unselected asthmatics (and, with a 6% 2-year mortality, we must assume that these subjects were sicker than most asthmatics). The evidence also strongly suggests that the subjects with low POD are at high risk of serious and fatal asthma. The relatively low $\beta$-agonist use in the low-POD population and their high ratio of hospitalizations to ED visits suggests that a relative lack of recognition of severe asthma, and consequently lack of adequate treatment, may have contributed to the unfortunate outcomes.

Magadle and associates are not the first to suggest that perception of dyspnea may be impaired in patients with asthma or even that such impairment may be related to the risk of death. Twenty-five years ago, Rubinfeld and Pain showed that asthmatics varied widely in their perception of methacholine-induced airways obstruction; soon thereafter, Burki and associates demonstrated similar findings in asthmatics exposed to external resistive loads. Twenty years ago, Hutchison and Olinsky showed that near-fatal asthma was associated with impaired respiratory drive; several investigators, notably Kikuchi et al in 1994, have shown that severe asthmatics with histories of life-threatening attacks tended to have lower-than-normal POD. The previous studies were retrospective, showing impaired POD after the fact of near-fatal asthma; Magadle and associates provide valuable new prospective information relating preexisting low POD to the risk of life-threatening asthma attacks, and demonstrate that dyspnea fails as a reliable early-warning sign of dangerous respiratory dysfunction.

The episodic nature of asthma means that cor pulmonale (and consequently bloating) is relatively uncommon, even though severe hypoxemia and even pulmonary hypertension might be present during attacks. Consequently, although “pink and puffing” is an apt description of the high-POD asthmatic during an attack, “dark and drowsy” rather than “blue and bloating” might more accurately describe the low-POD asthmatic. Regardless, the findings of Magadle and associates reemphasize that the blue asthmatics are more likely to die of asthma, but they do not show us why that is. Is it that blue bloaters slip more easily into carbon dioxide narcosis as their lung function worsens during an asthma attack, with the carbon dioxide retention and acidemia impairing respiratory muscle strength at the same time that hypoxemia suppresses central medullary respiratory drive more than their blunted carotid body chemoreceptors can respond to? Or is it that the impaired sensitivity of blue bloaters to the unpleasant sensations of excessive respiratory loads prevents them from summoning help early in the evolution of an
asthma attack and that their lack of evident discomfort prevents physicians and other caregivers from taking the attack seriously, allowing the airways obstruction to progress further than it would for a pink puffer?

These findings and these questions reemphasize the importance of making objective measurements of the severity of asthma, during and prior to attacks. Magadle and associates recommend determining POD, by measuring the dyspnea response to added external loads or to bronchoprovocation tests, in all asthmatics, allowing physicians to identify and focus scarce medical resources for monitoring and patient education in self-management on the subjects most at risk. Maybe so, but it seems that home peak flow monitoring and its correlation with symptom diaries would accomplish the same purpose more efficiently, inexpensively, and safely.

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Oropharyngeal Dysfunction in COPD Patients

The Need for Clinical Research

As chest physicians, we evaluate oropharyngeal function in patients in whom we suspect aspiration, including those with a history of stroke, Parkinson’s disease, motor neuron disease, myasthenia, myopathies and other central and peripheral nervous system diseases, and in patients with oropharyngeal structural abnormalities, selected systemic diseases, and recent endotracheal extubation. However, the association between pulmonary parenchymal diseases, including COPD, and oropharyngeal function has not been examined in a systematic manner. Swallowing is a complex physiologic process involving four consecutive phases (oral preparatory, oral voluntary, pharyngeal, and esophageal) utilizing > 30 muscles. The precise timing and coordination of swallowing is vital for bolus transfer into the esophagus and for airway protection. There is also an interdependence between respiration and swallowing that is under complex voluntary and involuntary control. In this issue of CHEST (see page 361), Mokhlesi et al hypothesize that patients with hyperinflation from COPD have altered oropharyngeal function, including a lower laryngeal resting position and a decrease in laryngeal elevation, potentially predisposing to aspiration. Utilizing videofluoroscopic techniques in 20 COPD patients and in 20 historical control subjects, the maximum laryngeal elevation during swallowing was significantly lower in the COPD patients. Patients with COPD also used spontaneous protective swallowing maneuvers more frequently than the historical control subjects. This preliminary study has design flaws, including the use of historical control subjects, and the potential presence of confounding variables. However, despite these flaws, the study does support the need for further research to determine whether COPD is associated with perturbed function of the oropharynx leading to episodes of aspiration. Whether these episodes have a role in COPD exacerbations and lung function decline remains to be determined.

What techniques are available to examine oropharyngeal function? The primary tool used by Mokhlesi